

REMARKS

Reconsideration of the application is requested in view of the amendment to the specification and claims and the remarks presented herein.

The claims in the application are claims 1 to 15, no other claims having been presented.

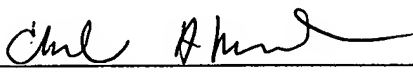
Claims 1 to 15 were rejected under 35 U.S.C. 112, second paragraph as being indefinite. The Examiner questioned what pK was and objected to “nucleofugal organic groups” as not being clear.

Applicants respectfully traverse these grounds of rejection as amended claim 1 recite pK as pK_a which is obvious to one skilled in the art since the value of the pK is 8.5 or more. The phrase “nucleofugal organic group” as it is an art recognized term as can be seen from the copy of IUPAC Compendium of Chemical Technology filed herewith where the definition of nucleofuge is given. Also submitted are pages 205 and 357 of Advanced Organic Chemistry, March wherein the term is well explained on page 205 and several examples of nucleofuge groups also known as leaving groups are given in Table 10.10. Therefore, the claims are definite and withdrawal of these grounds of rejection is requested.

In view of the amendments to the specification and claims and the above remarks, it is

believed that the claims clearly point out Applicants' invention. Therefore, favorable reconsideration of the application is requested.

Respectfully submitted,
Hedman and Costigan



Charles A. Muserlian, 19,683
Attorney for Applicants
Tel. # (212) 302 8989

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Enclosures

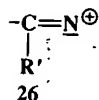
nucleofuge

A *leaving group* that carries away the bonding electron pair. For example, in the *hydrolysis* of an alkyl chloride, Cl^- is the nucleofuge. The tendency of atoms or groups to depart with the bonding electron pair is called nucleofugality. The adjective is nucleofugal.

See also *electrofuge*, *nucleophile*.

1994, 66, 1145

gen analogs of carbocations, can exist in this area than on carbocations. In and in the other (26) to only one atom.



e. Like carbenes and nitrenes, nitrenium

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A mechanism is the actual process by which a reaction takes place—which bonds are broken, in what order, how many steps are involved, the relative rate of each step, etc. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely. There is much about the fine details which is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases there are several proposed mechanisms, each of which completely explains all the data.

Types of Mechanism

In most reactions of organic compounds one or more covalent bonds are broken. We can divide organic mechanisms into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, though they usually do. The important thing is that the electrons are never unpaired. For most reactions it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book we shall always designate as the substrate that molecule that supplies carbon to the new bond. When carbon-carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which the attacking reagent. In heterolytic reactions the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. In a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free-radical mechanisms*.

les and Nitrenes, Ref. 239, pp. 297-357; Gassman
Lwowski Nitrenes, Ref. 239, pp. 405-419.

Br

 Br^-

ene reaction

any of the normal carbene reactions. This mechanism has been called the S_N1C_B . If the first step is an S_N1 step, the reaction is base-catalyzed.

order of ability to leave. The order-
N2 reactions.

mechanisms the leaving group departs at a slower rate. In the tetrahedral mechanism the leaving group is still intact during the nucleophilic attack so it still affects the reactivity in two ways. (1) The nature of X, the partial positive character of X, the greater the partial positive character of X, the greater the reactivity towards the nucleophile. (2) The nature of the leaving group in the tetrahedral intermediate **67** (p. 331) there is a negative charge on the oxygen atom. If X is a poorer leaving group than the starting compounds. Thus there is a higher energy barrier (loss of X) or back to starting materials. This increases the sequence of reactivity to be $\text{CONH}_2 > \text{RCONR}'_2 > \text{RCOO}^-$.³⁶¹ The increasing stability of the leaving-group decreases the effect and retard the rate for this reaction.

it fails to undergo many reactions for a special basic enough to take a proton from the acid.

TABLE 10.10 Leaving groups listed in approximate order of decreasing ability to leave. Groups that are common leaving groups at saturated and carbonyl carbons are indicated

Substrate RX	Common leaving groups	
	At saturated carbon	At carbonyl carbon
RN ₂ ⁺	×	
ROR ₂ ⁺		
ROSO ₂ C ₄ F ₉		
ROSO ₂ CF ₃	×	
ROSO ₂ F		
ROTs, etc. ^a	×	
RI	×	
RBr	×	
ROH ₂ ⁺	×	
RCI	×	×
RORH ⁺	×	×
RONO ₂ , etc. ^a	×	
RSR ₂ ^{+,363}		
RNR ₂ ⁺	×	
RF		
ROCOR ³⁶⁴	×	×
RNH ₃ ⁺		×
ROAr ³⁶⁵		×
ROH		×
ROR		×
RH		
RNH ₂		×
RAr		
RR		

*ROTs, etc., includes esters of sulfuric and sulfonic acids in general, for example, ROSO_2OH , ROSO_2OR , ROSO_2R , etc. RONO_2 , etc., includes inorganic ester leaving groups, such as $\text{ROPO}(\text{OH})_2$, $\text{ROB}(\text{OH})_2$, etc.

The Effect of the Reaction Medium³⁶²

The effect of solvent polarity on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged. For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.11³⁶⁶) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and

³⁶²For a monograph, see Reichardt *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988. For reviews, see Klumpp, Ref. 294, pp. 186-203; Bentley; Schleyer *Adv. Phys. Org. Chem.* **1977**, *14*, 1-67.

³⁰For a review of the reactions of sulfonium salts, see Knipe, in *Stirling The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 313-385. See also Badet; Julia; Lefebvre *Bull. Soc. Chim. Fr.* **1984**, 11-431.

1976, 24, 187-224.

^{34b}Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-ROCH₂(NO₂)₃] react at rates comparable to tosylates: Sinnott; Whiting *J. Chem. Soc. B* **1971**, 965. See also Page; Pritt; Whiting *J. Chem. Soc., Perkin Trans. 2* **1972**, 906.

³⁶⁶This analysis is due to Ingold *Structure and Mechanism in Organic Chemistry*, 2d ed.; Cornell University Press: Ithaca, NY, 1969, pp. 457-463.